

B1 concluded
terminus of C5a (SEQ. ID NO:1, C5a₆₅₋₇₄, ISHKDMQLGR) twice with I₆₅Y and H₆₇F (eg. 2) led to enhancement of agonist potency by about 2 orders of magnitude. These results are summarised in Table 2. Analyses of Ramachandran plots and 2D NMR spectra for compound 2 suggested that certain structural features, namely a twisted "helix-like" backbone conformation for residues 65-69 and a β -turn for residues 71-74, might be responsible for activity. These preliminary results provided some insight to structural requirements for tight binding to a C5a receptor.--

Pages 30 and 37, please replace Tables 2 and 4 as shown on the attached pages:

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--Table 2
Pharmacological Activity of C5a Agonist Analogues*

Peptide No.	Peptide	Fetal Artery EC ₅₀ (μM)	PMN Enzyme Release EC ₅₀ (μM)	Binding Affinity IC ₅₀ (μM)
SEQ. ID NO:1	C5a ₆₅₋₇₄ (ISHKDMQLGR)	>1000	>1000	>1000
SEQ. ID NO:2	YSFKDMQLGR	9.6	92	1.3
SEQ. ID NO:3	YSFKDMPLaR	0.5	72	3.7
SEQ. ID NO:4	YSFKPMPLaR	0.2	4.1	6.0
SEQ. ID NO:5	C5a ₃₇₋₄₆ -ahxYSFKPMPLaR	0.06	5.9	0.7
SEQ. ID NO:6	C5a ₁₂₋₂₀ -ahxYSFKPMPLaR	0.08	0.7	0.07
	C5a	0.02	0.03	0.0006

*Finch *et al*, 1997

Table 4
Receptor-Binding Affinities^a and Antagonist Activities^b in Human PMNs

Compound		Receptor Affinity ^a IC ₅₀ (μM)	Antagonist Potency ^b IC ₅₀ (μM)	Agonist Activity ^c
SEQ. ID NO:7	MeFKP(dCha)Wr	1.8 (15)	0.085 (9)	No
SEQ. ID NO:8	MeFKP(dCha)Wr-CONH ₂	14 (5)	0.5 (3)	No
SEQ. ID NO:9	MeFKP(dCha)WR	11 (5)	0.7 (3)	No
SEQ. ID NO:10	MeFKPLWR	144 (1)	>1000 (3)	nd
SEQ. ID NO:11	Ac-F-[KP(dCha)Wr]	3.2 (40)	0.090 (5)	No
SEQ. ID NO:12	Ac-F-[OP(dCha)Wr]	0.28 (6)	0.012 (4)	No
SEQ. ID NO:4	YSFKPMPLaR	6.0 ^d	-	Yes
SEQ. ID NO:1	C5a ₆₅₋₇₄ , ISHKDMLGR	>1000 ^e	-	-
	C5a	0.0008 (9)	-	Yes

Number of experiments in parenthesis. Corrected for amino acid content

Square brackets indicate cyclic portion.

nd= not determined

^a 50% reduction in binding of ¹²⁵I-C5a to intact human PMNs

^b 50% reduction in myeloperoxidase secretion from human PMNs mediated by 100 nM C5a

^c Agonist activity in dose range 0.1 nM-1 nM

^d Finch *et al*, 1997; ^e Kawai *et al*, 1991

Page 39, please replace the text beginning at line 6 through the end of the page as follows:

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Compound	n	R	Isomer*	Receptor Affinity μ M	Agonist Activity
SEQ. ID NO:13	1	H	S-	9	No
SEQ. ID NO:14			R-	34	No
SEQ. ID NO:15	2	H	S-	0.3	No
SEQ. ID NO:16			R-	3.7	No
SEQ. ID NO:17	3	Ac	S-	0.3	No
SEQ. ID NO:11		Ac	R-	38	No
SEQ. ID NO:18	4	Ac	S-	3.2	No
SEQ. ID NO:12		Ac	R-	51	No

Refers to stereochemistry of Arg side chain

Pages 41 and 42, please replace Table 6 as shown on the attached page:

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--Table 6

Effect of Cyclisation on Antagonist Binding Affinity and Antagonist Potency

PEPTIDE		pD ₂ ± SE ^a	IC ₅₀ (μM) ^a	(n)	pD ₂ ± SE ^b	IC ₅₀ (μM) ^b	(n)
SEQ. ID NO:11	AcF-[KpdChaWR]	5.49 ± 0.22	3.2	4	7.07 ± 0.29	0.09	5
SEQ. ID NO:18	AcF-[OPdChaWR]	6.44 ± 0.14*	0.4	9	7.30 ± 0.09	0.05	9
SEQ. ID NO:19	[FWPdChaWR]	4.37 ± 0.36*	43	3	nd		
SEQ. ID NO:20	AcF-[KmdChaWR]	4.81 ± 0.06	15	2	nd		
SEQ. ID NO:21	AcF-[KKdChaWR]	3.94 ± 0.4	116	3	4.88	13	1
Effect of length of linker in cycle on antagonist binding affinity and antagonist potency							
SEQ ID NO:22	AcF-[XPdChaWR]	5.02 ± 0.07	9.5	3	4.71 ± 0.23	20	3
SEQ ID NO:23	AcF-[X ² PdChaWR]	4.77 ± 0.14*	17	3	6.09 ± 0.08*	0.8	4
SEQ ID NO:11	AcF-[OPdChaWR]	4.60 ± 0.06*	16	4	6.42 ± 0.10	0.4	4
SEQ ID NO:24	AcKF-[OPdChaWR]	4.96 ± 0.03	11	3	6.73	0.2	1

Table 6 (cont.)

SEQ. ID NO:	PEPTIDE	pD ₂ ± Se ^a	IC ₅₀ (μM) ^a	(n)	pD ₂ ± SE ^b	IC ₅₀ (μM) ^b	(n)
SEQ. ID NO: 14	F-[XPdChaWR]	4.39 ± 0.10*	41	3	nd		
SEQ. ID NO: 16	F-[X ² PdChaWR]	5.42 ± 0.05	3.8	3	6.70 ± 0.04	0.4	3
SEQ. ID NO: 25	F-[OPdChaWR]	5.51 ± 0.07	3.1	3	5.79 ± 0.34*	1.6	3
SEQ. ID NO: 26	F-[KPdChaWR]	5.09 ± 0.08	8.1	3	5.55 ± 0.57*	2.8	3
Effect of L-Arg on antagonist binding affinity and antagonist potency							
SEQ. ID NO: 17	AcF-[OPdChaWR]	6.57 ± 0.05*	0.3	3	7.91 ± 0.17*	0.01	3
SEQ. ID NO: 13	F-[XPdChaWR]	4.98 ± 0.05	10	3	5.63 ± 0.13*	2.4	3
SEQ. ID NO: 15	F-[X ² PdChaWR]	6.50 ± 0.04*	0.3	5	7.36 ± 0.13	0.04	3
SEQ. ID NO: 27	F-[OPdChaWR]	7.21 ± 0.01*	0.06	3	7.41 ± 0.14	0.04	3
SEQ. ID NO: 28	F-[KPdChaWR]	6.50 ± 0.12*	0.3	4	6.69 ± 0.04	0.2	3